CHEMICALS UNDER CONSIDERATION FOR POSSIBLE LISTING AS DEVELOPMENTAL AND REPRODUCTIVE TOXICANTS (DARTs) VIA THE AUTHORITATIVE BODIES MECHANISM: 16 CHEMICALS IDENTIFIED BY US EPA

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The 16 chemicals listed in the table below may meet the criteria for listing under Proposition 65 via the authoritative bodies listing mechanism. The regulatory guidance for listing by this mechanism is set forth in Title 22, California Code of Regulations (CCR), Section 12306. For example, the regulations include provisions covering the criteria for evaluating the documentation and scientific findings by the authoritative body to determine whether listing under Proposition 65 is required.

US EPA has been identified as an authoritative body for purposes of Proposition 65 (22 CCR Section 12306(l)) and has identified the chemicals in the table below as causing developmental or reproductive toxicity. This was done by that Agency in implementing its Toxics Release Inventory (TRI) program (*i.e.*, Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 [EPCRA]). On the basis of identifying chemicals that caused reproductive, developmental and/or other toxicities the US EPA added a number of chemicals to the TRI list. The US EPA published its toxicity findings in the *Federal Register* (**59:**1788-1859, 1994 and **59:**61432-61485, 1994). In proposing specific chemicals for addition to the TRI list, the Agency stated that a hazard assessment was performed for each candidate, "…in accordance with relevant EPA guidelines for each adverse human health or environmental effect…" (*Federal Register* **59:**1790).

OEHHA has found that the chemicals in the table below have been "formally identified" as causing reproductive toxicity according to the regulations covering this issue (22 CCR 12306[d]) because the chemicals have "been identified as causing … reproductive toxicity by the authoritative body" (*i.e.*, US EPA) "in a document that indicates that such identification is a final action" (*i.e.*, the TRI *Final Rule* [*Federal Register* **59:**61432]) and have "been included on a list of chemicals causing … reproductive toxicity issued by the authoritative body" "and the document specifically and accurately identifies the chemical" and has been "published by the authoritative body in a publication, such as, but not limited to the federal register…"

OEHHA also finds that the criteria for "as causing reproductive toxicity" given in regulation (22 CCR 12306[g]) appear to have been satisfied for the chemicals in the table below. In making this evaluation, OEHHA relied upon the documents and reports cited

by US EPA in making their finding that the specified chemicals cause reproductive toxicity. In some cases, OEHHA consulted additional sources of information on the specific studies cited by US EPA. This was done only where necessary to affirm or clarify details of results and study design for studies cited by US EPA; OEHHA did not review additional studies not relied on by US EPA.

A major source of information used by the US EPA was the "Tox-Oneliner" database maintained by US EPA's Office of Pesticide Programs (OPP). This database consists of brief summaries of (usually unpublished) data submitted to the Agency in compliance with regulatory requirements. Many database entries include a notation of "core grade" – a system formerly used by US EPA to indicate the extent to which a study conformed to published test guidelines (US EPA 1983a and 1983b). Under this scheme, a "core grade guideline" study was considered to meet all guideline requirements; a "core grade minimum" study was considered sufficient for risk assessment; and a "core grade supplementary" study was considered to provide useful supplementary information, but not to be suitable for risk assessment on its own.

Chemical	CAS No.	Endpoints	Pesticide status or usage
Amitraz	33089-61-1	developmental toxicity	Registered in CA
Bromoxynil octanoate	1689-99-2	developmental toxicity	Registered in CA
Chlorsulfuron	6490-27-23	developmental toxicity female reproductive toxicity male reproductive toxicity	Registered in CA
Disodium cyano-dithiomidocarbo-nate	138-93-2	developmental toxicity	Registered in CA
Ethyl dipropyl-thiocarbamate	759-94-4	developmental toxicity	Registered in CA
Fenbutatin oxide	13356-08-6	developmental toxicity	Registered in CA
Metiram	9006-42-2	developmental toxicity	Registered in CA
Metribuzin	21087-64-9	developmental toxicity	Registered in CA
Nabam	142-59-6	developmental toxicity	Registered in CA
N-methyl-pyrrolidone (NMP)	872-50-4	developmental toxicity male reproductive toxicity female reproductive toxicity	Solvent
Potassium dimethyl-dithiocarbamate	128-03-0	developmental toxicity	Registered in CA

Chemical	CAS No.	Endpoints	Pesticide status or usage
Quizalofop-ethyl	76578-14-8	male reproductive toxicity	Not currently registered in CA
Sodium dimethyl-dithiocarbamate	128-04-1	developmental toxicity	Registered in CA
Tebuthiuron	34014-18-1	developmental toxicity	Registered in CA
Terbacil	5902-51-2	developmental toxicity	Not currently registered in CA
Thiophanate-methyl	23564-05-8	female reproductive toxicity male reproductive toxicity	Registered in CA

Studies cited by US EPA in making findings with regard to reproductive toxicity are briefly described below. The statements in bold reflect data and conclusions which appear to satisfy the criteria for sufficiency of evidence for reproductive toxicity in regulation (22 CCR 12306[g]). Where a notation of "not stated" has been made, OEHHA staff were unable to find an explicit statement of a particular detail such as the number of animals in each dose group. Where NOELs (no-observed-effect-level), LOELs (lowest-observed-effect-level), or LELs (lowest-effect-level) are included in this document, they are quoted directly from the cited references.

Amitraz (CAS No. 33089-61-1)

Developmental toxicity **has been manifested as decreased fetal viability and an increased frequency of morphological abnormalities.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: "…there is sufficient evidence for listing amitraz on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the …developmental toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993a) states, "A three-generation reproduction study in rats demonstrated increased mortality during suckling and decreased litter size. The fetotoxic LOAEL in this study was 5 mg/kg/day and the NOAEL was 1.6 mg/kg/day. In a teratology study in rabbits, a fetotoxicity LOAEL of 5 mg/kg/day, and NOAEL of 1 mg/kg/day was based on the incidence of cleft palate and meningocoele associated with small ears and displaced toe. Data from OPP's Tox-Oneliner database support these findings."

In the TRI final rule document (US EPA, 1994b) the agency responded to extensive comments on these studies by the regulated community. Both studies were reanalyzed, and the agency's original conclusions (US EPA, 1994a) reaffirmed. With regard to the multigeneration reproductive toxicity study, US EPA (1994b) concluded, "EPA's reanalysis of this data indicates that there was a decrease in litter size and pup survival at 5 mg/kg/day in all 3 generations and a slight reduction in pup weight in the F_1 and F_2 generations. Thus there was direct evidence of fetotoxicity." With regard to the rabbit teratology study, the agency concluded (US EPA, 1994b), "Upon reanalysis of the rabbit teratology study, EPA determined that although this study does not fully satisfy the guidelines for study conduct under FIFRA [*Federal Insecticide, Fungicide, Rodenticide Act*], it is sufficient for the purposes of hazard assessment, with a NOEL and LOEL for maternal and developmental toxicity of 5 and 25 mg/kg/day, respectively."

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat 3-generation reproductive toxicity study. Study rated as core grade minimum (US EPA, 1997b).
   Study b) rabbit teratology study. No core grade reported (US EPA, 1997b). According to the Final Rule document for additions to the TRI list (US EPA, 1994b), "…EPA determined that although this study does not fully satisfy the guidelines for study conduct under FIFRA, it is sufficient for the purposes of hazard assessment…" .

2. **Route of administration:**
   Study a) oral, diet.
   Study b) oral, gavage (CDPR, 1994).
3. **The frequency and duration of exposure:**
   Study a) daily from prior to mating of parental generation, throughout maturation and reproduction of subsequent generations.
   Study b) daily on each of gestation days 6 - 18.
4. **The numbers of test animals:**
   Study a) 20-24 females per group (CDPR, 1994).
   Study b) 8 - 10 pregnant animals per group (CDPR, 1994).
5. **The choice of species:**
   Rats and rabbits are standard species for use in toxicological studies.
6. **The choice of dosage levels:**
   Study a) 0, 15 (1.6 mg/kg), 50 (5.0 mg/kg), and 200 ppm.
   Study b) 0, 1, 5, 25 mg/kg/day.
7. **Maternal toxicity:**
   Study a) none noted in consulted documentation.
   Study b) The US EPA Tox-Oneliner on Amitraz (US EPA, 1990) states that a maternal LEL of 25 mg/kg was based on the frequency of abortion of entire litters. The NOEL for this endpoint was stated to be 5 mg/kg. However, in the absence of other indications of serious systemic toxicity in the dam, this endpoint is generally considered a manifestation of developmental toxicity.

Bromoxynil octanoate (CAS No. 1689-99-2)

Developmental toxicity **has been manifested in offspring as morphological abnormalities.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: "…there is sufficient evidence for listing bromoxynil octanoate on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the developmental toxicity data for bromoxynil and bromoxynil octanoate."

Supporting documentation for the TRI listing (US EPA, 1993b) states, "In a dermal teratology study, bromoxynil octanoate was teratogenic to rat fetuses… Teratogenic effects (hydrocephalus, micropthalmia, anopthalmia and severe defects in ossification of the skull) were observed in rabbits administered 60 mg/kg/day bromoxynil by gavage… Fetotoxicity (increases in all forms of supernumerary ribs) was observed in rats at 5 mg/kg/day… several other developmental studies indicate potential developmental toxicity of bromoxynil phenol."

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat dermal teratology study. Rated core grade supplemental, "pending submission of additional information" (US EPA, 1994c).
   Study b) rabbit teratology study on bromoxynil, rated core grade guideline (US EPA, 1997b).
   Study c) rat teratology study - No core grade reported in US EPA documents consulted.
2. **Route of administration:**
   Study a) dermal.
   Study b) oral, gavage.
   Study c) not stated in US EPA documents consulted.
3. **The frequency and duration of exposure:**
   Study a) daily on each of gestation days 6 - 15.
   Study b) not stated directly, but as this study was rated "core grade guideline" it would have met US EPA test guidelines (US EPA, 1983a) which require exposure on gestation days 6 - 15.
   Study c) not stated.
4. **The numbers of test animals:**
   Study a) 25 animals per dose group (US EPA, 1989a).
   Study b) not stated directly, but as this study was rated "core grade guideline" it would have met US EPA test guidelines (US EPA, 1983a) which require a minimum of 12 rabbits per dose group.
   Study c) not stated.
5. **The choice of species:**
   The rat and rabbit are standard species used in toxicological studies.
6. **The choice of dosage levels:**
   Study a) 0, 2, 5, 10, 15, 20, and 75 mg/kg/6hrs/day (US EPA, 1989a).
   Study b) 0, 30, and 60 mg/kg/day. As this study was rated core grade guideline, it would have met US EPA test-guideline standards (US EPA, 1983a), which require a minimum of three doses. Hence there was presumably at least one other dose-level tested.
   Study c) 0, 1.5, 5, 30 mg/kg/day.
7. **Maternal toxicity:**
   Study a) The maternal LOAEL, based on reduced body weight gain, was 20 mg/kg/day, with a corresponding NOAEL of 15 mg/kg/day. The LOAEL and NOAEL for developmental toxicity in this study were 15 and 10 mg/kg/day, respectively.
   Study b) IRIS (US EPA, 1997b) describes 30 mg/kg/day as both the NOEL and the LEL for maternal animals in this study. The endpoint of maternal toxicity is stated to be body weight loss. The developmental LEL, for

major malformations, in this study was 60 mg/kg/day, with a corresponding NOEL of 30 mg/kg/day.

Study c) the maternal LOEL, based on body weight loss, was 30 mg/kg/day. Developmental toxicity was observed at 5 mg/kg/day, with a NOEL of 1.5 mg/kg/day.

Chlorsulfuron (CAS No. 6490-27-23)

Developmental toxicity **was manifested as an increased frequency of fetal resorptions.** ***Male and female reproductive toxicity*** **were manifested as decreased fertility.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: "…there is sufficient evidence for listing chlorsulfuron on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental and reproductive toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993b) states, "In a rabbit developmental study, an increased incidence of fetal resorptions was observed at the LOEL of 75 mg/kg/day. The NOEL was 25 mg/kg/day… In a 3-generation rat reproduction study, a decrease in [the] fertility index was observed at 125 mg/kg/day (LOEL). The NOEL was 25 mg/kg/day…"

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rabbit developmental toxicity study, graded core minimum (US EPA, 1990).
   Study b) rat 3-generation reproductive toxicity study, graded core guideline (US EPA, 1990).
2. **Route of administration:**
   Study a) not stated directly, but as this study was rated "core grade minimum" it would have met US EPA test guidelines (US EPA, 1983a) which specify exposure by the oral route.
   Study b) oral, diet.
3. **The frequency and duration of exposure:**
   Study a) not stated directly, but as this study was rated "core grade minimum" it would have met US EPA test guidelines (US EPA, 1983a) which require exposure on gestation days 6 - 15.
   Study b) daily from 103 days prior to mating, through subsequent study generations (US EPA, 1990).

4. **The numbers of test animals:**
   Study a) not stated directly, but as this study was rated "core grade minimum" it would have met US EPA test guidelines (US EPA, 1983a) which specify a minimum of 12 pregnant rabbits per dose group.
   Study b) not stated directly, but as this study was rated "core grade guideline" it would have met US EPA test guidelines (US EPA, 1983b) which specify a minimum of 20 animals per dose group.
5. **The choice of species:**
   Rats and rabbits are standard test species used in toxicity testing.
6. **The choice of dosage levels:**
   Study a) 0, 10, 25, 75 mg/kg/day (US EPA, 1990).
   Study b) 0, 100, 500, 2500 ppm in the feed (US EPA, 1990). US EPA (1993b and 1994a) expressed the LOEL and NOEL for this study in mg/kg/day, but details of the conversion method were not provided.
7. **Maternal toxicity:**
   Study a) not mentioned.
   Study b) a LEL of 2500 ppm (125 mg/kg/day) and a NOEL of 500 ppm (25 mg/kg/day) were determined for decreased maternal body weight. These levels were the same as those determined for decreased fertility.

Disodium cyanodithiomidocarbonate (CAS No. 138-93-2)

Developmental toxicity **was manifested as increased skeletal variations and increased resorptions.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that, "there is sufficient evidence for listing disodium cyanodithioimidocarbonate on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental toxicity data."

Supporting documentation for the TRI listing (US EPA, 1993b) states, “Rats administered disodium cyanodithiomidocarbonate by gavage on gestation days 6 to 15 demonstrated increased skeletal variations in offspring. The NOEL is 6 mg/kg, LEL is 18 mg/kg. In a rabbit teratology study, increased resorptions were observed in rabbits administered the compound by gavage on gestation days 6 - 18. The NOEL is 3 mg/kg, LEL is 10 mg/kg."

Stakeholder comments on the TRI proposed-listing document (US EPA, 1994a) contended that the skeletal variations and increased resorptions observed with disodium cyanodithiocarbonate exposure should not be considered as evidence of developmental toxicity. The Agency disagreed with these comments, and reaffirmed their previous conclusion (US EPA, 1994b).

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat developmental toxicity study. Data are described as 'adequate' (US EPA,1994e).
   Study b) rabbit developmental toxicity study. Data are described as 'adequate' (US EPA,1994e).
2. **Route of Administration:**
   Study a) oral, gavage.
   Study b) oral, gavage.
3. **The frequency and duration of exposure:**
   Study a) daily on gestation days 6 - 15.
   Study b) daily on gestation days 6 - 18.
4. **The numbers of test animals:**
   Not stated for either study. However, numbers were considered sufficient for a designation of 'adequate' in the Reregistration Eligibility Document (US EPA, 1994e). US EPA test guidelines (1983a) require a minimum of 20 rats or 12 rabbits per dose group
5. **The choice of species:**
   The rat and rabbit are standard species used in toxicology testing.
6. **The choice of dosage levels:**
   Study a) 0, 2, 6, 18 mg/kg/day.
   Study b) 0, 3, 10, or 30 mg/kg/day
7. **Maternal toxicity:**
   Study a) both maternal and developmental toxicity had a LOEL of 18 mg/kg/day and a NOEL of 6 mg/kg/day (US EPA, 1994e).
   Study b) both maternal and developmental toxicity had a LOEL of 10 mg/kg/day and a NOEL of 3 mg/kg/day (US EPA, 1994e).

Ethyl Dipropylthiocarbamate (CAS No. 759-94-4)

Developmental toxicity **has been manifested as increased resorptions, growth retardation, and decreased body weights.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: "…there is sufficient evidence for listing ethyl dipropylthiocarbamate (EPTC) on the EPCRA section 313 list pursuant to EPCRA section 313(d)(2)(B) based on the available …reproductive toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993a) states, "An increased incidence of fetal resorptions, increased incidence of fetal retardations, and decreased fetal body weights were observed in rats receiving 300 mg/kg/day on days 6-15 of

gestation. The LOEL was 300 mg/kg/day and the NOEL was 100 mg/kg/day (US EPA, 1993[c]). In a 2-generation rat reproduction study, decreased pup weight was observed in both generations at 40 mg/kg/day. The NOEL was 10 mg/kg/day (US EPA, 1993[d])."

The rat teratology study is summarized by both IRIS (US EPA, 1993d) and the Tox-Oneliner database (US EPA, 1993c). The frequencies of fetal resorption and growth retardation were increased, and fetal weights were decreased at a dose of 300 mg/kg/day. No morphological abnormalities were noted at 300 mg/kg/day, and no other adverse developmental effects were noted at doses of 100 or 30 mg/kg/day.

The reproductive toxicity study is summarized by IRIS (US EPA, 1993d), the results for adult toxicity serving as the basis for the oral RfD. Reduced pup weights were noted in both the F1 and F2 generations, at the highest concentration tested of 800 ppm (40 mg/kg/day). It should be noted that, while US EPA cites reproductive toxicity as the basis for addition to the TRI list, developmental toxicity is the appropriate basis for addition to the Proposition 65 list.

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat teratology study - stated to be core grade minimum (US EPA, 1985; US EPA, 1997b).
   Study b) rat 2-generation study - US EPA (1997b) lists the study as core grade minimum.
2. **Route of administration:**
   Study a) oral gavage.
   Study b) oral, in diet.
3. **The frequency and duration of exposure:**
   Study a) each of gestation days 6-15.
   Study b) continuous, in diet.
4. **The numbers of test animals:**
   Study a) not stated. However, US EPA test guidelines (1983a) require a minimum of 20 rats per dose group.
   Study b) 30 per sex in each dose group.
5. **The choice of species:**
   The rat is a standard species used in toxicology testing.
6. **The choice of dosage levels:**
   Study a) 0, 30, 100, 300 mg/kg/day.
   Study b) 0, 50, 200, 800 ppm (0, 2.5, 10, 40 mg/kg/day).

7. **Maternal toxicity:**
   Study a) maternal toxicity, manifested as increased mortality, reduced body weight gain, and reduced food consumption, occurred at the same dose as developmental toxicity.
   Study b) parental toxicity, consisting of reduced body weights and weight gains, as well as an increased incidence of degenerative cardiomyopathy, occurred at the intermediate and high doses (200 and 800 mg/kg/day). Effects on offspring weight were observed at the high dose of 800 ppm.

Fenbutatin oxide (CAS No. 13356-08-6)

Developmental toxicity **has been manifested as intrauterine lethality and decreased viability.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that: "…there is sufficient evidence for listing fenbutatin oxide on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993b) states, "In a rat teratology study, the LOEL for developmental toxicity (toxic to zygote) was 60 mg/kg/day and the NOEL was 30 mg/kg/day…. In a rabbit teratology study, oral administration of 5 mg/kg/day produced intrauterine lethality and was also toxic to maternal animals. The NOEL was 1 mg/kg/day…. In a 3-generation rat reproduction study, administration of 15 mg/kg/day (LOEL) produced [a] decreased viability index. The NOEL was 5 mg/kg/day."

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat teratology study, classified core minimum.
   Study b) rabbit teratology study, classified core minimum.
   Study c) 3-generation rat reproduction study, not rated, but appears to meet FIFRA guidelines.
2. **Route of administration:**
   Study a) not stated, but US EPA (1983a) test guidelines specify the oral route of exposure.
   Study b) oral.
   Study c) not stated, but US EPA (1983b) specify the oral route as standard.

3. **The frequency and duration of exposure:**
   Study a) not stated, but US EPA (1983a) test guidelines specify exposure daily, on each of gestation days 6 -15 for rats.
   Study b) daily, on gestations days 6 - 18 (US EPA, 1994d).
   Study c) not stated, but US EPA test guidelines for reproductive toxicity studies (US EPA, 1983b) require at least one generation to be exposed continuously from the prenatal period through sexual maturation and a round of reproduction.
4. **The numbers of test animals:**
   Study a) not stated, but US EPA (1983a) guidelines specify at least 20 pregnant rats per dose group.
   Study b) not stated, but US EPA (1983a) guidelines specify at least 12 pregnant rabbits per dose group.
   Study c) not stated, but US EPA (1983b) guidelines specify the use of sufficient animals to ensure at least 20 pregnant females per dose group.
5. **The choice of species:**
   Rats and rabbits are standard species for use in toxicological studies.
6. **The choice of dosage levels:**
   Study a) the only doses stated are the LOEL of 60 mg/kg/day and the NOEL of 30 mg/kg/day. In order to meet guideline standards (US EPA, 1983a), there must have also been an untreated control group, and at least one additional dose group.
   Study b) 0, 1, 5, and 10 mg/kg/day (US EPA, 1994d).
   Study c) the only doses stated are the LOEL of 15 mg/kg/day and the NOEL of 5 mg/kg/day. In order to meet guideline standards (US EPA, 1983b) there would have to have been at least an untreated control group, and one additional dose level.
7. **Maternal toxicity:**
   Study a) not mentioned.
   Study b) there was evidence of both maternal and developmental toxicity at the same dose level of 5 mg/kg/day. 1 mg/kg/day was a NOEL for both maternal and developmental toxicity.
   Study c) not mentioned.

Metiram (CAS No. 9006-42-2)

Developmental toxicity **was evidenced by delayed ossification of the parietal bone in rat pups prenatally exposed to ethylene thiourea, a metabolite of metiram.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "… there is sufficient evidence for listing metiram on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the … developmental toxicity data for ethylenethiourea, a metabolite and degradation product of metiram."

Supporting documentation for the TRI listing (US EPA, 1993a) states, "Metiram is an ethylenebisthiocarbamate fungicide. Evidence suggests that ethylenebisthiocarbamate fungicides and ethylenethiourea (a common contaminant, metabolite, and degradation product of these fungicides) cause adverse developmental toxicity in experimental animals. … A NOAEL of 5 mg/kg has been reported for ethylenethiourea, based on results from a rat developmental toxicity study. Ethylenethiourea caused delayed ossification or hardening of the parietal bone in pups." According to the US EPA Special Review Document on EBDCs (US EPA, 1989b), "Animal metabolism of the EBDCs is rapid and ETU and ethylene bisdiisothiocyanate sulfide (EBIS) are major metabolites."

In the final notice of intent to deny applications for registration of EBDC fungicides, US EPA (1992b) states, "The no-observable-adverse-effect level (NOAEL) for developmental toxicity resulting from exposure to ETU is equal to or less than 5.0 mg/kg/day based on a rat study … ETU was shown to be developmentally toxic at dose levels lower than those that produced no apparent maternal toxicity. At 5.0 mg/kg/day, which was the lowest dose tested, developmental toxicity was observed in the form of delayed ossification or hardening of the parietal bone (in the skull). Delayed ossification was clearly dose-related at higher rates than in control and appears to be a sensitive indicator of exposure to ETU … The results of the NTP study conducted on rats and mice indicated that ETU affected thyroid function in both species. However, a mouse study showed no developmental toxicity at very high doses (800 mg/kg/day by gavage). Therefore, simple inhibition of the thyroid gland may not necessarily be the mechanism by which developmental effects are manifested in rats. Preliminary evidence in the literature indicates developmental effects in rabbits." These studies appear to be the same as those referred to in the TRI documentation.

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   US EPA (1989b) used these studies in the Agency's 'Special Review' process for evaluating the risks posed to humans and the environment by EBDCs and ethylenethiourea. The Agency considered the data suitable for this purpose.
2. **Route of administration:**
   Study a) rat developmental toxicity study - oral.,
   Study b) mouse developmental toxicity study - oral gavage.,
   Study c) rabbit developmental toxicity study - not stated.
3. **The frequency and duration of exposure:**
   Study a) daily from prior to pregnancy through gestation day 15, or daily on gestation days 6 through 15.
   Study b) not stated.
   Study c) not stated.

4. **The numbers of test animals:**
   Not stated for any study.
5. **The choice of species:**
   Rats, mice, and rabbits are all standard species for developmental and reproductive toxicity testing.
6. **The choice of dosage levels:**
   Study a) 5.0 mg/kg/day was the lowest dose tested.
   Study b) 0, 200, 400, 800 mg/kg/day.
   Study c) not stated.
7. **Maternal toxicity:**
   Study a) US EPA (1992b) states, "ETU was shown to be developmentally toxic at dose levels lower than those that produced no apparent maternal toxicity."
   Study b) not relevant as the study was considered to be negative.
   Study c) not stated.

Metribuzin (CAS No. 21087-64-9)

Developmental toxicity **was manifested as growth retardation and minor skeletal abnormalities.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "…there is sufficient evidence for listing metrabuzin on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the … developmental toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993b) states, "In a rabbit teratology study, the NOEL for maternal and fetotoxicity was 15 mg/kg/day, and the LOEL was 45 mg/kg/day… In a[nother] rabbit teratology study, developmental effects including irregular spinus process and decreased pup body weight were observed in rats treated with metribuzin (Sencor) during gestation day 7-19 at 85 mg/kg/day. The NOEL for developmental toxicity was 30 mg/kg/day."

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) core grade guideline (US EPA, 1986),
   Study b) core grade minimum.
2. **Route of administration:**
   Not stated for either study, but US EPA test guidelines for developmental toxicity studies (US EPA, 1983a) specify the gavage route of exposure. As both of these studies received acceptable grades, it is presumed that guideline requirements were met.
3. **The frequency and duration of exposure:**
   Study a) not stated, but US EPA test guidelines for developmental toxicity studies (US EPA, 1983a) specify daily dosing on each of gestation days 6 - 18 for rabbits. As the study was considered to meet guideline requirements, it is presumed that this requirement was met.
   Study b) stated to have been daily on gestation days 7 - 19.
4. **The numbers of test animals:**
   Not stated for either study, but US EPA test guidelines for developmental toxicity studies (US EPA, 1983a) specify a minimum of 12 rabbits per dose group. As both of these studies received acceptable grades, it is presumed that guideline requirements were met.
5. **The choice of species:**
   The rabbit is a standard species for use in toxicological studies.
6. **The choice of dosage levels:**
   Study a) 0, 15, 45, 135 mg/kg/day.
   Study b) 0, 10, 30, 85 mg/kg/day.
7. **Maternal toxicity:**
   Study a) LEL = 45 mg/kg/day, NOEL = 15 mg/kg/day.
   Study b) LOEL = 30 mg/kg/day, NOEL = 10 mg/kg/day.

Nabam (CAS No. 142-59-6)

Developmental toxicity **was evidenced by delayed ossification of the parietal bone in rat pups prenatally exposed to ethylene thiourea, a metabolite of nabam.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "… there is sufficient evidence for listing nabam on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the … developmental toxicity data for ethylenethiourea, a metabolite and degradation product of nabam."
Supporting documentation for the TRI listing (US EPA, 1993a) states, "Nabam is an ethylenebisthiocarbamate fungicide. Evidence suggests that ethylenebisthiocarbamate fungicides and ethylenethiourea (a common contaminant, metabolite, and degradation product of these fungicides) cause adverse developmental toxicity in experimental animals… A NOAEL of 5 mg/kg has been reported for ethylenethiourea, based on results from a rat developmental toxicity study. Ethylenethiourea caused delayed ossification or

hardening of the parietal bone in pups." According to the US EPA Special Review Document on EBDCs (US EPA, 1989b), "Animal metabolism of the EBDCs is rapid and ETU and ethylene bisdiisothiocyanate sulfide (EBIS) are major metabolites."

In the final notice of intent to deny applications for registration of EBDC fungicides, US EPA (1992b) states, "The no-observable-adverse-effect level (NOAEL) for developmental toxicity resulting from exposure to ETU is equal to or less than 5.0 mg/kg/day based on a rat study… ETU was shown to be developmentally toxic at dose levels lower than those that produced no apparent maternal toxicity. At 5.0 mg/kg/day, which was the lowest dose tested, developmental toxicity was observed in the form of delayed ossification or hardening of the parietal bone (in the skull). Delayed ossification was clearly dose-related at higher rates than in control and appears to be a sensitive indicator of exposure to ETU… The results of the NTP study conducted on rats and mice indicated that ETU affected thyroid function in both species. However, a mouse study showed no developmental toxicity at very high doses (800 mg/kg/day by gavage). Therefore, simple inhibition of the thyroid gland may not necessarily be the mechanism by which developmental effects are manifested in rats. Preliminary evidence in the literature indicates developmental effects in rabbits." These studies appear to be the same as those referred to by the TRI documentation.

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   US EPA (1989b) used these studies in the Agency's 'Special Review' process for evaluating the risks posed to humans and the environment by EBDCs and ethylenethiourea. The Agency considered the data suitable for this purpose.
2. **Route of administration:**
   Study a) rat developmental toxicity study - oral.
   Study b) mouse developmental toxicity study - oral gavage.,
   Study c) rabbit developmental toxicity study - not stated.
3. **The frequency and duration of exposure:**
   Study a) daily from prior to pregnancy through gestation day 15, or daily on gestation days 6 through 15.
   Study b) not stated.
   Study c) not stated.
4. **The numbers of test animals:**
   Not stated for any study.
5. **The choice of species:**
   Rats, mice, and rabbits are all standard species for developmental and reproductive toxicity testing.
6. **The choice of dosage levels:**
   Study a) 5.0 mg/kg/day was the lowest dose tested.

Study b) 0, 200, 400, 800 mg/kg/day.
Study c) not stated.

7. **Maternal toxicity:**
   Study a) US EPA (1992b) states, "ETU was shown to be developmentally toxic at dose levels lower than those that produced no apparent maternal toxicity."
   Study b) not relevant as the study was considered to be negative.
   Study c) not stated.

N-methylpyrrolidone (NMP) (CAS No. 872-50-4)

Male reproductive toxicity **has been manifested as reductions in the male fertility index in a multigeneration study in rats.**
Female reproductive toxicity **has been manifested as reductions in the female fecundity index in a multigeneration study in rats.**
Developmental toxicity **has been manifested as resorptions, malformations, reduced litter size, reduced postnatal survival and reduced pup body weight in experimental animals.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that, "...there is sufficient evidence for listing N-methylpyrrolidone on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental and reproductive toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993a) states, "In a two-generation reproductive study, there was evidence of reproductive [toxicity] in the F1 generation [in rats] after exposure to 50 mg/kg/day (LOAEL; no NOAEL was established). In addition, exposure to 500 mg/kg/day resulted in an increased incidence of dams with decreased corpora lutea. There was also evidence of developmental toxicity in both generations after exposure to 500 mg/kg/day as demonstrated by reduced litter size, reduced postnatal survival, and reduced pup weight.

"Maternal toxicity (significant reduction in mean body weight gain) was observed in rabbits receiving 175 mg/kg by gavage on days 6 through 18 of gestation (the NOAEL was 55 mg/kg/day). Exposure to 540 mg/kg/day (LOAEL) resulted in developmental toxicity as demonstrated by a significant increase in resorptions, and malformations (misshapen skull bone and cardiovascular malformations). The NOAEL for developmental toxicity was 175 mg/kg/day."

The reference cited by the TRI supporting documentation (US EPA, 1993e) concluded that, "Reproductive and developmental studies in animals exposed to NMP showed effects including reduced fertility and reduced mean offspring body weight at birth and throughout lactation. These effects in animals suggest that similar effects may occur in humans. … Exposure to 540 mg/kg resulted in developmental toxicity as demonstrated by

a significant increase in resorptions, and malformations (misshapen skull bone and cardiovascular malformations). … There was evidence of reproductive toxicity in the F1 generation after exposure to doses as low as 50 mg/kg, the lowest dose tested. Exposure to 50 mg/kg or more resulted in significant reductions in the male fertility index and the female fecundity index. In addition, exposure to 500 mg/kg resulted in an increased incidence of dams with decreased corpora lutea. There was also an increased incidence of males with atrophied testes, but it is not clear whether the number affected was statistically significant. There was also evidence of developmental toxicity in both generations after exposure to 500 mg/kg as demonstrated by reduced litter size, reduced survival, and reduced pup body weight."

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design**:
   In responding to comments on the TRI proposed rule, US EPA (1994b) concluded, "The review of the 2-generation rat reproductive study by an independent reviewer did not find fault with the entire study but stated that it should not be used for risk assessment purposes. EPA agrees with this judgment but is not using this study for risk assessment purposes, but rather *as an indication of human health hazard* [emphasis added] … The Agency believes that despite the flaws in the study, the data described above clearly show evidence of developmental toxicity. In addition, EPA believes that the body of evidence supports the finding that NMP is uniquely toxic to the developing fetus…".
2. **Route of administration:**
   Study a) oral, gavage
   Study b) oral, diet.
3. **The frequency and duration of exposure**:
   Study a) rabbit gavage teratology study- daily exposure, days 6-18 gestation.
   Study b) rat multigeneration feeding study- 10 days prior to mating and continuing throughout mating, gestation and lactation for both generations.
4. **The numbers of test animals**:
   Study a) 15-20/group.
   Study b) 30/sex/group.
5. **The choice of species**:
   Rabbits are standard test species for developmental toxicology studies and rats are a standard species for reproductive toxicology studies.
6. **The choice of dosage levels**:
   Study a) 0, 55, 175, or 540 mg NMP/kg bw/day.
   Study b) 0, 50, 160, 500 mg NMP/kg diet.
7. **Maternal toxicity:**

Study a) maternal toxicity was reported as decreased food intake during dosing and decreased weight gain during dosing at 175 and 540 mg NMP/kg bw/day.
Study b) maternal toxicity was reported as reduced food intake, body weight and/or body weight gain in the F0 and F1 generations at the 500 mg NMP/kg diet dose.

Potassium dimethyldithiocarbamate (CAS No. 128-03-0)

Developmental toxicity **was manifested as skeletal abnormalities, increased postimplantation loss, and decreased fetal weights in rabbits exposed prenatally.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "… there is sufficient evidence for listing potassium dimethyldithiocarbamate on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental toxicity data for this chemical."

It should be noted that the statement in the final rule document (US EPA 1994b) which cites 'neurological toxicity' as the basis for listing was an editing error (US EPA, 1997a). The concluding statement should have read 'developmental toxicity'.

Supporting documentation for the TRI listing (US EPA, 1993b) states, "New Zealand White rabbits given 38 mg/kg/day by gavage on days 6 to 18 of gestation exhibited malalignment of sternebrae, total postimplantation loss ($p<0.01$) and fetal weight decrement. Also at this dose level various possible malformations including adactyly, gastroschisis, short tail, anal atresia, spina bifida, atelectasis, costal cartilage anomaly, vertebral anomaly with/without rib, caudal vertebrae anomaly, and severe sternebrae malalignment in 6/52 fetuses from 5/11 litters. At the 77 mg/kg/day dose level, there was severe fetal/embryo lethality. The NOEL was 12.8 mg/kg/day."

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CFR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   The rabbit developmental toxicity study was considered to be core minimum (US EPA, 1989c).
2. **Route of administration:**
   Oral, gavage.
3. **The frequency and duration of exposure:**
   Daily, on gestation days 6 - 18.
4. **The numbers of test animals:**
   20 pregnant rabbits per group.
5. **The choice of species:**

Rabbits are a standard species in toxicological testing.

6. **The choice of dosage levels:**
   0, 12.8, 38, or 77 mg active ingredient/kg bw.
7. **Maternal toxicity:**
   NOEL: 12.8 mg active ingredient/kg bw. LEL: 38 mg active ingredient/kg/day for clinical signs, and at the HTD (highest tolerated dose) [77 mg/kg/day] body weight-gain decrement and reduced food consumption. Possible increased maternal death and abortions at 38 mg active ingredient/kg/day and above.

Quizalofop-ethyl (CAS No. 76578-14-8)

Male reproductive toxicity **has been manifested as testicular atrophy in dogs.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "…there is sufficient evidence for listing quizalofop-ethyl on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available reproductive … toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993b) states, "In a 6-month dietary dog study, 10 mg/kg/day produced testicular atrophy in males. The NOEL was 2.5 mg/kg/day."

US EPA (1993b) cites the 1993 tox-oneliner for the dog study. OEHHA obtained a more recent version of the tox-oneliner on quizalofop-ethyl (US EPA, 1996), which includes the Agency's previous assessment of the dog study.

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   The 6-month feeding study conducted in dogs was considered to have met guideline requirements (US EPA, 1996).
2. **Route of administration:**
   Oral, diet.
3. **The frequency and duration of exposure:**
   Continuous for 6 months.
4. **The numbers of test animals:**
   Not directly stated, but study was considered to meet guideline requirements.
5. **The choice of species:**
   Dogs are a standard species used in toxicology testing.
6. **The choice of dosage levels:**
   0, 25, 100, and 400 ppm in the diet.

7. **Maternal toxicity:**
   Not relevant.

Sodium dimethyldithiocarbamate (CAS No. 128-04-1)

Developmental toxicity **was manifested as skeletal abnormalities, increased postimplantation loss, and decreased fetal weights in rabbits exposed prenatally to potassium dimethyldithiocarbamate. In solution, the active component, *i.e.*, the dimethyldithiocarbamate ion, is present for both the sodium and potassium salts.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "…there is sufficient evidence for listing sodium dimethyldithiocarbamate on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental toxicity data for potassium dimethyldithiocarbamate."

Supporting documentation for the TRI listing (US EPA, 1993b) states, "New Zealand White rabbits given 38 mg/kg/day by gavage on days 6 to 18 of gestation exhibited malalignment of sternebrae, total postimplantation loss ($p<0.01$) and fetal weight decrement. Also at this dose level various possible malformations including adactyly, gastroschisis, short tail, anal atresia, spina bifida, atelectasis, costal cartilage anomaly, vertebral anomaly with/without rib, caudal vertebrae anomaly, and severe sternebrae malalignment in 6/52 fetuses from 5/11 litters. At the 77 mg/kg/day dose level, there was severe fetal/embryo lethality. The NOEL was 12.8 mg/kg/day."

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   The rabbit developmental toxicity study was considered to be core grade minimum (US EPA 1989c).
2. **Route of administration:**
   Oral, gavage.
3. **The frequency and duration of exposure:**
   Daily, on gestation days 6 - 18.
4. **The numbers of test animals:**
   20 pregnant rabbits per group.
5. **The choice of species:**
   Rabbits are a standard species in toxicological testing.
6. **The choice of dosage levels:**
   0, 12.8, 38, or 77 mg active ingredient/kg bw.
7. **Maternal toxicity:**
   NOEL: 12.8 mg active ingredient/kg bw. LEL: 38 mg active ingredient/kg/day for clinical signs, and at the HTD (highest tolerated dose)

[77 mg/kg/day] body weight-gain decrement and reduced food consumption. Possible increased maternal death and abortions at 38 mg active ingredient/kg/day and above.

Tebuthiuron (CAS No. 34014-18-1)

Developmental toxicity **has been manifested as suppression of growth in rats and rabbits.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that, "... there is sufficient evidence for listing tebuthiuron on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993a) states, "Administration of 25 mg/kg/day (LOEL) on days 6 through 18 of gestation produced reduced body weights in offspring of rabbits. The NOEL was 10 mg/kg/day. .... In a 3-generation rat reproduction study, decreased body weight was observed in the offspring of animals administered 20 mg/kg/day (LOEL). No NOEL was established and the study was not classified." It should be noted that the decreased offspring weights observed in the 3-generation study were identified at weaning of pups which had been suckled by continuously-exposed dams. Hence the effects could have resulted from postnatal exposure, prenatal exposure, or a combination of pre- and postnatal exposure. This is not the case for the rabbit developmental toxicity study, where the animals were exposed only during specified days of gestation. Additional studies cited by the TRI supporting documentation pertain to growth deficits with exposure limited to the postnatal period. Those studies are not considered here.

The TRI supporting documentation (US EPA, 1993a) in turn cites IRIS (US EPA, 1992a) and the Tox-Oneliner database (US EPA, 1992c). Concerning the rabbit developmental toxicity study, the Tox-Oneliner database states that the developmental LEL was 25 mg/kg/day, for reduced fetal body weights. According to this source, the NOEL for developmental effects was 10 mg/kg/day. IRIS provides only a 'teratogenic' NOEL of 25 mg/kg/day, with no LEL for this endpoint. Presumably IRIS (US EPA, 1992a) is using the designation, 'teratogenic', only in the sense of morphological defects.

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design**:
   Study a) rabbit developmental toxicity study - classified 'core grade minimum'.
   Study b) rat 3-generation reproduction study - not graded.

2. **Route of administration:**
   Study a) not stated - but US EPA test guidelines for developmental toxicity studies (US EPA, 1983a) specify the oral route of exposure. Presumably these criteria would have been met by a study graded 'core minimum'.
   Study b) not stated.
3. **The frequency and duration of exposure**:
   Study a) oral, gavage, on each of gestation days 6-18 (US EPA, 1992c).
   Study b) not stated.
4. **The numbers of test animals**:
   Study a) 15 adult female rabbits per dose group (US EPA, 1988b).
   Study b) not stated.
5. **The choice of species**:
   Rats and rabbits are standard species used in developmental and reproductive toxicity testing.
6. **The choice of dosage levels**:
   Study a) 0, 10, 25 mg/kg/day [the lack of a 3rd dose group may be the reason why the study was graded 'core minimum', rather than 'core guideline'].
   Study b) 0, 400 ppm [20 mg/kg/day], 800 ppm (HDT).
7. **Maternal toxicity:**
   Study a) the maternal NOEL was stated to be > 25 mg/kg/day.
   Study b) the systemic NOEL for this study was considered to be 800 ppm (the HDT), while the reproductive NOEL was < 400 ppm [20 mg/kg/day], based on decreased body weights of pups at weaning.

Terbacil (CAS No. 5902-51-2)

Developmental toxicity **was manifested as reduced viability and reduced body weights in offspring of exposed experimental animals.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "…there is sufficient evidence for listing terbacil on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available … developmental toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993b) states, "Decreases in the number of implantations and live fetuses, were observed in rats administered 62.5 mg/kg/day (LOEL) orally on days 6-15 of gestation. The NOEL was 12.5 mg/kg/day (24 [US EPA, 1994c]). Significantly reduced body weights were observed in the offspring of rabbits orally administered 600 mg/kg/day (LOEL) orally on days 6-15 [sic] of gestation. The NOEL was 200 mg/kg/day (24 [US EPA, 1994c], 11 [US EPA , 1993d]). The studies were classified Core Minimum."

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) rat developmental toxicity study - classified core grade minimum.
   Study b) rabbit developmental toxicity study - classified core grade minimum.
2. **Route of administration:**
   Study a) oral.
   Study b) oral.
3. **The frequency and duration of exposure:**
   Study a) daily on gestation days 6 - 15.
   Study b) daily on gestation days 7 - 19 (US EPA, 1988a).
4. **The numbers of test animals:**
   Study a) not stated, but study was considered to meet guideline requirements, which specify a minimum of 20 pregnant rats per dose group (US EPA, 1983a).
   Study b) 18 animals per dose group (US EPA, 1988a).
5. **The choice of species:**
   Rats and rabbits are standard species for developmental toxicity testing.
6. **The choice of dosage levels:**
   Study a) 0, 250, 1250, 5000 ppm.
   Study b) 0, 30, 200, or 600 mg/kg/day.
7. **Maternal toxicity:**
   Study a) maternal LEL = 1250 ppm for reduced body weight, maternal NOEL = 250 ppm.
   Study b) maternal LEL = 600 mg/kg/day for increased mortality, decreased weight gain, and clinical signs of toxicity; maternal NOEL = 200 mg/kg/day.

Thiophanate-methyl (CAS No. 23564-05-8)

Male reproductive toxicity **was evidenced by decreased spermatogenesis in rats.** ***Female reproductive toxicity*** **was manifested as reduced numbers of implantations in mice, and reduced litter weights in rats.**

The US Environmental Protection Agency (US EPA, 1994a and 1994b) concluded that "…there is sufficient evidence for listing thiophanate-methyl on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the reproductive toxicity data for this chemical."

Supporting documentation for the TRI listing (US EPA, 1993a) states, "Decreased spermatogenesis was observed in male rats fed diets containing 32 mg/kg/day thiophanate-methyl; the NOEL was 8mg/kg/day (IRIS, 1993 [US EPA, 1993d]). Based

on the NOEL for decreased spermatogenesis, an oral RfD of 0.08 mg/kg/day was derived (IRIS, 1993 [US EPA, 1993d]); the confidence in the study, database, and RfD was rated high. ... In a 3-generation reproductive study in rats, reduced litter weights were seen at a daily dietary dose of 32 mg/kg thiophanate-methyl. The NOEL was 8 mg/kg/day. A decrease in the number of implantations was observed in mice administered a limit dose of 1,000 mg/kg/day."

With regard to the studies cited as supporting US EPA's action in adding a chemical to the EPCRA-TRI list, OEHHA finds that the evidence for DART effects appears to meet the criteria of 22 CCR 12306, and notes the following:

1. **Adequacy of the experimental design:**
   Study a) 2-year rat feeding study. Rated core grade minimum. The study was used as the principal study in determining the oral RfD for thiophanate-methyl. Confidence in the study was rated as high, "The principal study appears to be of high quality and is given a high rating." (US EPA, 1992a).
   Study b) 3-generation rat reproductive toxicity study. The study was graded 'core minimum' (US EPA, 1992a).
   Study c) limit test. The study was rated 'core grade supplemental' (US EPA, 1992a).
2. **Route of administration:**
   Study a) oral, feed.
   Study b) oral, feed.
   Study c) not stated.
3. **The frequency and duration of exposure:**
   Study a) daily in feed for 2 years.
   Study b) not stated, but US EPA test guidelines for reproductive toxicity studies (US EPA, 1983b) specify continuous exposure from prior to mating of the parental generation, throughout gestation and lactation, and continuing through postnatal development and reproduction of the F1 generation to produce the F2. As the study was considered to meet guideline requirements, it is presumed that this dosing schedule was adhered to. As the study was stated to involve 3 generations, dosing was presumably continued for F2 animals though production of the F3 generation.
   Study c) not stated.
4. **The numbers of test animals:**
   Study a) 35 males and 35 females per dose group. 50 males and 50 females served as controls.
   Study b) not stated, but US EPA test guidelines for reproductive toxicity studies (US EPA 1983b) specify sufficient animals to ensure a minimum of 20 pregnant animals per dose group. As the study received an acceptable grade, it is presumed that guideline requirements were met.
   Study c) not stated.
5. **The choice of species:**

Rats and mice are standard species for reproductive toxicity testing.

6. **The choice of dosage levels:**

   Study a) 0, 10, 40, 160, or 640 ppm.

   Study b) 0, 8, 32 mg/kg/day. As the study was rated 'core grade minimum' (US EPA, 1993d), there was presumably at least one additional dose level, which would have been required to meet US EPA test guideline standards for a reproductive toxicity study (US EPA, 1983b).

   Study c) 1000 mg/kg/day.

7. **Maternal toxicity:**

   Study a) not relevant.

   Study b) not stated.

   Study c) not stated.

References

California Department of Pesticide Regulation (CDPR, 1994). *Summary of Toxicology Data. Amitraz.* California Environmental Protection Agency, CDPR, Medical Toxicology Branch.

Registry of Toxic Effects of Chemical Substances (RTECS, 1993). National Institutes of Health, National Library of Medicine, Bethesda, MD.

US Environmental Protection Agency (US EPA, 1983a). *Health Effects Test Guidelines; Teratogenicity Study.* Office of Toxic Substances, Office of Pesticides and Toxic Substances.

US Environmental Protection Agency (US EPA, 1983b). *Health Effects Test Guidelines; Reproduction and Fertility Effects.* Office of Toxic Substances, Office of Pesticides and Toxic Substances.

US Environmental Protection Agency (US EPA, 1985). *Tox-Oneliner Database (sanitized version)*, Office of Pesticide Programs, Arlington, VA.

US Environmental Protection Agency (US EPA, 1986). *Tox-Oneliner Database (sanitized version)*, Office of Pesticide Programs, Arlington, VA.

US Environmental Protection Agency (US EPA, 1988a). *Health Advisory for Terbacil*. US EPA Office of Drinking Water, Washington DC.

US Environmental Protection Agency (US EPA, 1988b). *Tebuthiuron.* Health Advisory Office of Drinking Water. US EPA, Washington D.C. 20460.

US Environmental Protection Agency (US EPA, 1989a). *Data Evaluation Report - Developmental toxicity (Embryo-fetal toxicity and teratogenicity potential) Study of Bromoxynil Octanoate administered percutaneously to Crl:CD (SD) BR presumed pregnant rats.* US EPA Office of Pesticide Programs, Washington DC.

US Environmental Protection Agency (US EPA, 1989b). Ethylene bisdithiocarbamates (EBDCs); Notice of Intent to Cancel; Conclusion of Special Review. *Federal Register* **57:**7484.

US Environmental Protection Agency (US EPA, 1989c). *Tox-Oneliner Database (sanitized version)*, Office of Pesticide Programs, Arlington, VA.

US Environmental Protection Agency (US EPA, 1990). *Tox-Oneliner Database (sanitized version)*, Office of Pesticide Programs, Arlington, VA.

US Environmental Protection Agency (US EPA, 1992a). *Integrated Risk Information System.* US EPA, Washington, DC.

US Environmental Protection Agency (US EPA, 1992b). *Ethylene bisdithiocarbamates (EBDCs); Notice of final determination; Notice of Intent to Cancel; Conclusion of Special Review.* Federal Register **57**:7484.

US Environmental Protection Agency (US EPA, 1992c). *Tox-Oneliner Database (sanitized version),* Office of Pesticide Programs, Arlington, VA.

US Environmental Protection Agency (US EPA, 1993a). *Support Document for the Health and Ecological Toxicity Review of TRI Expansion Chemicals.* US EPA Office of Pesticide Programs, Washington, DC.

US Environmental Protection Agency (US EPA, 1993b). *Support Document for the Addition of Chemicals from Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) Active Ingredients to EPCRA Section 313.* US EPA Office of Pesticide Programs, Washington, DC.

US Environmental Protection Agency (US EPA, 1993c). *Tox-Oneliner Database (sanitized version),* Office of Pesticide Programs, Arlington, VA.

US Environmental Protection Agency (US EPA, 1993d). *Integrated Risk Information System.* US EPA, Washington DC.

US Environmental Protection Agency (US EPA, 1993e). Letter from Charles Auer to Mr. John Kneiss. Synthetic Organic Chemical Manufacturers Association. (with attachment: *Lifecycle Analysis and Pollution Prevention Assessment for N-Methylpyrrolidone (NMP) in Paint Stripping,* pages 1-95, September 8, 1993.)

US Environmental Protection Agency (US EPA, 1994a). Proposed Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. *Federal Register* **59**: 1788.

US Environmental Protection Agency (US EPA, 1994b). Final Rule: Addition of Certain Chemicals; Toxic Chemical Release Reporting; Community Right to Know. *Federal Register* **59**(229): 61432.

US Environmental Protection Agency (US EPA, 1994c). *Tox-Oneliner Database (sanitized version),* Office of Pesticide Programs, Arlington, VA.

US Environmental Protection Agency (US EPA, 1994d). *Reregistration Eligibility Decision (RED): Fenbutatin-oxide.* US EPA, OPPTS. Washington D.C. 20460.

US Environmental Protection Agency (US EPA, 1994e). *Reregistration Eligibility Decision (RED): Disodium cyanodithiomidocarbonate (DCDIC).* US EPA Office of Pesticide Programs and Toxic Substances, Washington, DC.

US Environmental Protection Agency (US EPA, 1996). *Tox-Oneliner Database (sanitized version)*, Office of Pesticide Programs, Arlington, VA.

US Environmental Protection Agency (US EPA, 1997a). Letter from Dr. Maria Doa, Chief, Toxics Release Inventory Branch, OPPTS, US EPA, to Dr. James Donald, Reproductive and Cancer Hazard Assessment Section, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, dated May 22, 1997.

US Environmental Protection Agency (US EPA, 1997b). *Integrated Risk Information System.* U.S. EPA, Washington DC.